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Predicting placebo analgesia - literature review and new perspectives

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Placebo responses are reliably caused by active neurobiological processes, including prefrontal-striatal-brainstem interactions and involvement of endogenous neurochemicals. Placebo analgesia is the best-studied type of placebo effect; the systems involved overlap with those involved in substance use and mental health disorders. Definitive studies of the brain and genetic predictors of individual differences the strength of the placebo effect remain to be performed. Such studies are crucial for harnessing placebo effects and placebo responses in clinical trials. In this review, we summarize current research on placebo analgesia and discuss promising new approaches. Placebo responses have been associated with genetic polymorphisms in several neurotransmitter systems, primarily opioids, dopamine, cannabinoids, and serotonin. However, these studies have generally been small and underpowered, and have focused on a few candidate genes, raising questions about their replicability and clinical utility. One promising emerging approach combines systems-level fMRI-based signatures (potential endophenotypes) and GWAS in twins. The twin design provides heritability estimates and permits genetic correlation analyses. In a *data fusion* approach, brain features with the highest genetic overlap can be examined using large-scale consortium data—including the ENIGMA and UK Biobank samples—to investigate phenotype-relevant brain-genetic associations at scale. New results using this approach have challenged previous work on pain genetics, and identified new, replicable genetic associations.